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Why do some women with epilepsy use valproic acid despite current guidelines? A single-center cohort study

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ABSTRACT

Objective: Current guidelines and regulations strongly discourage the use of valproic acid (VPA) in women of childbearing age because of the risk of congenital malformations and neurodevelopmental disability in children exposed to VPA in utero. Our goal was to establish the reasons for continued use of VPA in a cohort of women with epilepsy (WWE) and to characterize the subgroup of WWE who do not consent to withdraw VPA despite potential risks.

Material and methods: The study included consecutive adult premenopausal WWE who visited an outpatient epilepsy clinic between April 2017 and March 2018. Data on demographics (age, age at onset of epilepsy), characteristics of epilepsy (types and frequency of seizures), and its treatment were collected from medical records and seizure diaries. All WWE taking VPA were regularly informed about VPA-related risks and had the opportunity to discuss the withdrawal of VPA.

Results: The study involved 353 WWE (mean age: 31.7 years). Focal epilepsy was diagnosed in 244 (69.1%) patients; 180 (51.0%) women had no seizures during last 12 months before the study visit, and 228 patients (64.6%) were on monotherapy. A total of 146 (41.3%) patients used VPA in the past, and 98 (27.8%) never used VPA. Of women who were currently on VPA ($n = 109$, 30.9%), 30 had concurrent severe disabilities that would make future pregnancy extremely unlikely, in further 15 patients, VPA was recommenced because of failure of alternative treatment and 64 women did not accept the plan of VPA withdrawal. Women currently on VPA were more likely to have genetic generalized epilepsy and to be on monotherapy (both $p \ll 0.001$). Among 64 WWE who decided to continue therapy with VPA, 35 (55.5%) had generalized epilepsy and 35 (55.5%) were in remission, 27 (42.2%) had at least one child, 9 (14.1%) planned to have a child in the near future but only 15 (23.4%) used effective contraception.

Conclusion: Treatment with VPA is unavoidable in many WWE of childbearing age despite recent regulations. About 60% of WWE currently treated with VPA do not consent to withdraw VPA treatment after thorough consideration of potential risks and other 40% use VPA because pregnancy is highly unlikely and/or other treatments failed.

1. Introduction

Valproate medicines (valproic acid, sodium valproate, valproate semisodium — further collectively referred to as VPA) have been used for decades as an effective treatment for epilepsy, prophylaxis of migraine, and bipolar disorder. However, the incidence of congenital malformations is much higher in children exposed to VPA in utero (10.7%) than among children of women with epilepsy (WWE) in general (7.1%) and of healthy women (2.3%) [1]. Also, the risk of major congenital malformations after in utero exposure to antiepileptic drugs (AEDs) used in monotherapy is higher for VPA (10.3%) than for several other commonly used AEDs (e.g., 2.9% for lamotrigine or 2.8% for levetiracetam), as shown in the most recent study based on EURAP registry [2]. Accumulating evidence from observational studies and pregnancy registers [2–4] led to the increasing awareness of potential teratogenicity. Moreover, the impact of VPA on neurodevelopment of children exposed to the drug in utero, including lower intelligence quotient, as well as worse verbal and memory abilities, became evident [5,6].

In 2014, European Medicines Agency (EMA) issued warnings on the use of VPA in girls and women of childbearing age [7] and recommended that VPA for epilepsy and bipolar disorder should be prescribed only if other treatments are ineffective or not tolerated.

Consequently, the use of VPA declined in many countries [8–10], but those measures were considered inadequate and led to another EMA statement [11] including a ban on the use of such medicines for migraine or bipolar disorder during pregnancy and a ban on the use of

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VPA to treat epilepsy during pregnancy, unless there is no other effective treatment available. According to that statement, 'valproate medicines must not be used in any woman or girl able to have children unless the conditions of a new pregnancy prevention programme are met'.

The recent change of paradigm related to the management of epilepsy with VPA seems challenging for both WWE and physicians who treat them. It seems obvious that treatment-naïve WWE would not receive VPA, if an effective alternative exists. There is a large subgroup of women, however, who either cannot be successfully treated with any other AED or decide to continue treatment with VPA after the thorough consideration of potential risks. The latter subgroup has not been described adequately yet.

Therefore, we studied the cohort of WWE managed in a single tertiary epilepsy outpatient clinic to establish the reasons for continued use of VPA against recent recommendations and to characterize the subgroup of WWE who do not consent to withdraw treatment with VPA despite the potential risks.

2. Material and methods

2.1. Patients

This cohort study recruited consecutive patients with epilepsy who visited the outpatient epilepsy clinic at the Department of Neurology within University Hospital in Krakow (Poland) between April 2017 and March 2018. All patients treated in the outpatient clinic were adults (i.e., aged at least 18 years). The inclusion criteria consisted of female sex and the diagnosis of epilepsy established according to the International League Against Epilepsy (ILAE) guidelines [12]. Women after menopause were excluded.

Study protocol followed the principles of Helsinki Declaration and was approved by the bioethical committee of the Jagiellonian University of Krakow. Each patient was informed about the aim and methods of the study and gave the written informed consent to participate. All eligible patients agreed to participate.

2.2. Procedures and definitions

Variables related to epilepsy included age at the diagnosis of epilepsy and the type of epilepsy established according to the data from history, neurological examination, electroencephalography, and neuroimaging (magnetic resonance imaging or computed tomography if magnetic resonance imaging was contraindicated). The type of epilepsy was classified in accordance with the recent ILAE position paper on classification of epilepsies (generalized, focal, combined generalized and focal, or unknown) [13]. The onset of epilepsy was defined as the occurrence of first-ever seizure. Frequency of seizures within the year preceding the first visit during the study period was established according to the data included in the seizure diaries and categorized into (1) more than 1 seizure per month; (2) 1–12 seizures per year; or (3) less than one seizure per year (the last one considered as remission). Additionally, we have analyzed the occurrence of tonic–clonic seizures (patients with myoclonic seizures only were formally not in remission but the lack of tonic–clonic seizures might be additional factor that could affect patient's decision upon VPA withdrawal). The type and the number of AEDs used at the time of the assessment were noted; the daily dose of VPA was also recorded.

According to the European and ILAE guidelines [7,14], each girl or woman of childbearing age treated in our outpatient clinic because of epilepsy received standardized extensive printed information on the potential risks related to the use of VPA in pregnancy and on the need for use of effective contraception. Also, risks and benefits were thoroughly discussed in those WWE who were currently on VPA, including legal representatives of those who could not made informed decisions because of intellectual disability. Such a discussion was also initiated during each subsequent visit. In most patients, those discussions and decisions were made before the initiation of the current study.

During the first visit within the study period, patients were informed about the aim and methods of the study. After the informed consent to participate was signed, each patient was asked to fill the questionnaire with the questions related to the VPA use and reproductive life. The following categories of VPA use were established: (1) used previously but withdrawn; (2) never used; (3) currently used. Among those who used VPA currently, the following three subgroups were discerned: (a) patients in whom the VPA withdrawal and switch to another AED failed, either due to the recurrence of seizures or due to significant side effects of other AED intended to replace VPA (e.g., rash after lamotrigine or depression after levetiracetam); (b) patients, in whom the severity of epilepsy and/or concomitant neurological disorder makes pregnancy unlikely (e.g., tetraplegia, institutional care due to severe physical or intellectual disability, very frequent seizures) and VPA was considered to provide better control of seizures than other AEDs; (c) patients who do not consent to withdraw of VPA despite the comprehensive discussion about the teratogenicity of the drug repeated during each visit (e.g., patients who gave birth to healthy child while on VPA or those who were less afraid of the potential teratogenic effects of VPA than of the recurrence of seizures). Questions related to reproductive life issues included information about children born and planned. Patient's approach to contraception was categorized as follows: (1) the use of effective contraception (oral hormonal contraception or intrauterine device) or (2) noneffective contraception, no contraception at all, or sexual abstinence, either as a personal choice or as a result of the severity of the disease related to epilepsy.

2.3. Statistical analysis

Variables were characterized either with means and standard deviations (SDs), median and interquartile range (according to distribution), or percentages. A χ^2 test was used to test the significance of the differences between the qualitative data (Fisher exact test was used in comparisons with small absolute number of cases). Differences between the normally distributed variables were tested with the Student *t*-test, and analysis of variances (or Kruskal–Wallis test) was used to compare more than two groups. The differences between groups revealed by analysis of variances were further evaluated with Tukey post hoc test.

A p-value of less than 0.05 was considered as significant. All the analyses were performed using Statistica v. 12.5 (StatSoft Inc., Tulsa, OK).

3. Results

This study involved 353 WWE. The mean age of participants was 31.7 years (SD: 7.7; range: 18–53), and the mean age at onset of epilepsy was 14.9 years (SD: 9.5). Table 1 provides data on general characteristics of epilepsy and its treatment among studied patients. Focal epilepsies were more prevalent; nearly half of the studied women had no seizures within the year preceding the study visit.

A total of 98 WWE (27.8%) never used VPA, and 146 (41.3%) patients used VPA in the past. One hundred and nine women (30.9%) were currently treated with VPA. Median dose of VPA in this group was 1000 mg (interquartile range: 600–1500 mg; range: 150–3000 mg).

Women who currently used VPA were younger at the onset of epilepsy than their counterparts who did not use VPA. They had generalized seizures or combination of generalized and focal seizures more often. Also, they were less likely to use AED in monotherapy (Table 2).

Among 109 women who currently used VPA, 30 (27.5%) were affected with severe disability, either physical or intellectual, that made future pregnancy unlikely. Further 15 patients (13.8%) had to recommence the treatment with VPA because its replacement with other AED(s) led either to loss of efficacy or to unacceptable side effects. Finally, the largest subgroup of patients (n = 64; 58.7%) consisted of

Table 1
Characteristics of epilepsy and its treatment among studied premenopausal women with epilepsy (n = 353).

	n (%)
Type of seizures	
Generalized	98 (27.8%)
Focal	244 (69.1%)
Mixed	10 (2.8%)
Unknown	1 (0.3%)
Frequency of seizures	
More than one per month	99 (28.0%)
1–12 per year	74 (21.0%)
Remission (no seizures in the past 12 months)	180 (51.0%)
Convulsive seizures	66 (18.7%)
Number of currently used AEDs	
1	228 (64.6%)
2	89 (25.2%)
3	30 (8.5%)
4	5 (1.4%)
5	1 (0.3%)
Patients having at least one child	131 (37.1%)
Patients planning to have a child in the near future	56 (15.9%)
Patients currently using effective contraception	73 (20.7%)

AED — antiepileptic drug; VPA — valproic acid or related compounds.

women who, despite repeated discussions of possible risks, made informed decision about the continued use of VPA. Table 3 provides comparisons of those three distinct subgroups in terms of characteristics of their epilepsy. Women who chose to continue treatment with VPA against guidelines were much less likely to have convulsive seizures, were older at the onset of epilepsy, and more often had focal seizures than their counterparts who used VPA either because of lack of other effective treatment or extremely low probability of pregnancy. Median dose of VPA was the highest in the subgroup of patients in whom pregnancy was considered highly unlikely, moderate among those who decided to continue treatment with VPA, and the lowest among women in whom the other treatments failed (Table 3).

Among 64 women who continued treatment with VPA after reconsideration of possible risks and benefits, 27 (42.2%) had at least one child, 9 (14.1%) planned to have a child in the near future, and 15 (23.4%) used effective contraception. Less than 5% had convulsive seizure within the year preceding the study, and fear of recurrent seizures was the reason given universally for the continued treatment with VPA.

4. Discussion

Management of chronic diseases, such as epilepsy, requires good cooperation between patient and treating physician. It includes shared decision-making with the thorough discussion of possible benefits and risks of each treatment option. The subgroup of patients who do not wish to withdraw the specific treatment (e.g., VPA) poses a great challenge for treating physicians. Our results show that about 30% of women of childbearing age still use VPA for several reasons, even though current guidelines strongly discourage such a management. While the continuing treatment with VPA in about 40% of that cohort is considered as justified and supported by the circumstances (either lack of efficacy of other AEDs or extremely low probability of pregnancy), further 60% of women in that group (or 18.1% of all premenopausal WWE) do not agree to withdraw treatment with VPA.

We are not aware of any study that would characterize specifically WWE who decided to continue treatment with VPA despite current guidelines. It is widely recognized, however, that the use of VPA among pregnant WWE is in steady decline over the past two decades, as evidenced, e.g., by UK and Ireland Epilepsy and Pregnancy register [15]. Valproic acid, either in mono- or polytherapy, was used by about 1% of pregnant WWE in the US study of pregnancy outcomes, which enrolled patients between 2012 and 2016 [16]. In a population of women in reproductive age (16–44 years) in Ireland, VPA accounted for 28% of all prescribed AEDs in 2008 and for 20% in 2013 [8]. In our cohort, studied in the context of the recent regulations, 30.9% of women of childbearing age were still treated with VPA. It may be expected that this proportion will slowly decline over years, as the treatment-naïve patients most probably will not receive VPA, but the expectations that the use of VPA will be reduced markedly should be viewed as improbable unless the drug itself is withdrawn from the market. In support of this notion, the recent study from Stockholm showed that the number of patients with epilepsy in whom treatment with VPA was initiated declined before the EMA warning in 2014, but was more or less stable in subsequent years [9]. It may suggest that those who could switch to alternative treatment had already done it, and the further decline is less probable. According to the most recent data, VPA is still most often prescribed AED in Poland (38% of all reimbursed AEDs used for epilepsy and psychiatric disorders between January and May 2018) [17]. Newer AEDs, e.g., levetiracetam or lamotrigine have been reimbursed as first-line treatment since 2012, and oxcarbazepine — since 2016. Thus, many women in the past years received VPA as a first monotherapy because of financial limitations, and this particular situation may change soon.

The characteristics of the subgroup of women who still want to be treated with VPA reveals some interesting features. About two-thirds of them use VPA in monotherapy (in contrast to other women who are treated with VPA), and the convulsive seizures occur in less than 5% of that subgroup. The fear of recurrent seizures was stated by those patients as a major reason for their decisions. About 14% of women who opted for continued treatment with VPA planned to have a child in the near future. Yet, only 23.4% of our patients from the same subgroup (and less than 21% of the whole cohort) used effective contraception. Those proportions are even lower than those suggested by the most recent questionnaire study of general population in Poland (33.2% [18]). Studies from other countries suggest marked variability in the use of oral contraceptives among WWE. They were prescribed in less than 10% of women of childbearing age and with epilepsy in Ireland in 2013 [8] and in 26% of WWE who took potentially teratogenic AEDs [19]. On the other hand, Herzog et al. [20] reported that almost 70% of WWE and at risk of unintended pregnancy used effective contraceptive methods. The personal choice regarding the use of contraceptives is influenced by the financial, social, and religious factors. This means also that many patients would not accept the policy to use an effective contraception even in the view of potential teratogenicity. While it may be argued that the awareness of the teratogenic effects of AEDs is relatively low among WWE [21] and that they often do not receive any counseling on this topic [22], the situation is different here, as each patient received detailed written information on these issues. Current guidelines suggest that 'women of childbearing potential who

Table 2
Comparison of women currently treated versus not treated with valproate medicines.

	Women taking VPA N = 109	Women not taking VPA N = 244	p-Value for the difference
Age	31.9 (SD: 7.4)	31.7 (SD: 7.8)	0.81
Age at onset of epilepsy	13.4 (SD: 8.7)	15.6 (SD: 9.8)	0.050
Type of seizures			
Generalized	47 (43.2%)	51 (20.9%)	≪0.001
Focal	54 (49.5%)	190 (77.9%)	≪0.001
Mixed	8 (7.3%)	2 (0.8%)	0.001
Unknown	0	1 (0.4%)	–
Frequency of seizures			
Remission	52 (47.7%)	128 (52.4%)	0.41
Convulsive seizures	25 (22.9%)	41 (16.8%)	0.17
Monotherapy	53 (48.6%)	175 (71.7%)	≪0.001
Patients having at least one child	36 (33.0%)	95 (38.9%)	0.29
Patients planning to have a child in the near future	11 (10.1%)	45 (18.4%)	0.047
Patients currently using effective contraception	23 (21.1%)	50 (20.5%)	0.90

VPA — valproic acid or related compounds.

Table 3
Comparison of subgroups of women currently treated with valproate medicines.

	VPA recommenced after the failed treatment with other AEDs N = 15 (Group A)	VPA due to conditions that make pregnancy unlikely N = 30 (Group B)	VPA continued according to the personal choice N = 64 (Group C)	p-Value for the difference
Age	34.5 (SD: 5.3)	30.7 (SD: 7.6)	31.9 (SD: 7.6)	0.25[a]
Age at onset of epilepsy	13.9 (SD: 4.5)	6.9 (SD: 5.7)	16.5 (SD: 9.0)	≪0.001[b]
Type of seizures				
Generalized	12 (80%)	22 (73.3%)	35 (55.5%)	≪0.001[c]
Focal	3 (20%)	8 (26.7%)	28 (44.5%)	
Mixed	0	0	0	
Unknown	0	0	0	
Remission	10 (66.7%)	7 (23.3%)	35 (55.5%)	0.004[d]
Convulsive seizures	3 (20%)	19 (63.3%)	3 (4.8%)	≪0.001[e]
Monotherapy	5 (33.3%)	7 (23.3%)	41 (65.1%)	≪0.001[f]
Daily dose of VPA, mg; median (interquartile range)	600 (600–1000)	1500 (1000–2000)	1000 (600–1000)	≪0.001[g]

VPA — valproic acid or related compounds; AED — antiepileptic drug; SD — standard deviation.
[a] One-way ANOVA: $F_{2,105} = 1.38$;.
[b] One-way ANOVA: $F_{2,60} = 15.82$; Tukey post-hoc test: group A vs. group B, $p = 0.014$; group A vs. group C, $p = 0.47$; group B vs. group C, $p \ll 0.001$.
[c] Pearson $\chi^2 = 46.99$; df = 2.
[d] Pearson $\chi^2 = 10.84$; df = 2.
[e] Pearson $\chi^2 = 39.28$; df = 2.
[f] Pearson $\chi^2 = 36.00$; df = 2.
[g] Kruskal–Wallis test; H = 16.08.

are not planning pregnancy and who continue treatment with valproate should utilize effective contraception methods or otherwise ensure that unplanned pregnancies can be avoided' [14]. In everyday practice, however, neurologists often face the dilemma whether to continue treatment with VPA in a patient who does not agree to withdraw it and does not use an effective contraception or to withdraw otherwise effective treatment (both scenarios leading to potential serious consequences).

The interpretation of our findings is somehow limited because of the inclusion of patients seen in tertiary epilepsy clinic — the population studied may be not representative to all patients with epilepsy. It should be noted, however, that we have included consecutive WWE, and the only exclusion criterion (being a woman after menopause) was strictly related to the clinical question studied. Moreover, in contrast to many studies using internet-based approach or other forms of interviewing, all potential subjects agreed to participate and were evaluated during visits in the epilepsy clinic.

Future studies should also involve data from population of women who receive VPA for indications other than epilepsy (i.e., migraine prophylaxis or bipolar disorder). Available data show that the use of VPA among WWE was in steady decline even before the recent regulation, but it declined sharply among women without epilepsy [9]. It may reflect the different speed of VPA withdrawal according to the indications (e.g., slow and careful withdrawal in patients with epilepsy versus more rapid tapering off in patients with migraine). It is less likely that the awareness of VPA-related teratogenicity varies among healthcare professionals in relation to the indication but, if proven, might be the goal to the future information campaigns.

We follow the general guideline of ILAE [14] stating that 'for female patients already established on valproate, it is also important to allow the patient to state a preference as to whether to continue the valproate. In most such cases, it may be appropriate to continue valproate when the patient prefers to do so'. Clinicians are well aware of the variety of circumstances that may impede the implementation of apparently simple dichotomous rules regarding the decision-making in patients with epilepsy. The regulatory decision was an important step towards the management of unfavorable pregnancy outcomes related to exposure to VPA. Now, it is time to reconsider the approach to those WWE who would most probably need VPA treatment for many years to come [23]. We hope that the characterization of that relatively large group of patient would contribute to that discussion.

5. Conclusions

Treatment with VPA is unavoidable in many WWE of childbearing age despite recent regulations. About 60% of WWE currently treated with VPA do not consent to withdraw VPA treatment after thorough consideration of potential risks, and other 40% use VPA because pregnancy is highly unlikely and/or other treatments failed.

Declaration of Competing Interest

MB received honoraria for publications from Sanofi-Genzyme; honoraria for lectures, travel expenses and conference fees from Sanofi, Adamed, Teva Pharmaceutical, Neuraxpharm, Glenmark, UCB Pharma.

AS received honoraria for lectures from Bayer, Boehringer Ingelheim, Novartis, Polpharma, Bristol-Myers Squibb, Novartis, Biogen, Teva Pharmaceutical, Medtronic; for the participation in advisory meetings from Bayer, Boehringer Ingelheim, Novartis.

WT received honoraria for publications from Sanofi-Genzyme; honoraria for lectures, travel expenses, and conference fees from Shire and CSL Behring.

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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